

were submitted to state-of-the art large-scale proteomic analyses. In silico systems biology was employed to identify key pathways in the studied processes.

Results: MK-801-treated astrocytes, and especially MK-801-treated oligodendrocytes displayed several proteins differentially expressed which overlapped with previous findings of schizophrenia human brains. On the other hand, MK801-treated neurons displayed very few differences in their proteome, an overlap with previous findings in human brain tissue below 10%. More interestingly, the dysregulation of glycolytic enzymes in MK801-treated oligodendrocytes are very similar to our observations in schizophrenia brain tissue, corroborating with recent findings about the importance of oligodendrocytes in the energy status of the brain. In oligodendrocytes, antipsychotics displayed differences in translational machinery and eIF2 signaling. Findings on cerebral organoids also showed overlaps with previous postmortem data, mainly on synaptic proteins and specially energy metabolism-associated pathways.

Discussion: These findings hold potential for the investigation of developmental and evolutionary features of schizophrenia brains and provides targets to be drug-screened as well as leads to the schizophrenia pathobiology.

25.4 PROMOTING MYELIN REPAIR RESCUES MICE FROM SCHIZOPHRENIA-LIKE BEHAVIOR INDUCED BY SOCIAL ISOLATION

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Background: Although pathological and genetic evidence suggest that oligodendrocyte (OL) or myelin deficits are associated with schizophrenia, the contribution of OL/myelin deficits to its etiology has not been clearly dissected, because OL/myelin abnormalities may be a concomitant phenomenon during the pathogenesis of schizophrenia.

Methods: Using olig2 ablation specifically in OLs (olig2 CKO) mice, we detected myelin development status and animal behaviors under normal condition or subjected to social isolation. We also examined the therapeutic effect of FDA-approved compounds, like quetiapine (an APD) or clemastine (a histamine antagonist) on animal behaviors.

Results: Our results demonstrated that deleting of olig2 led to impaired development of OLs and myelin deficit from postnatal day14 (P14) to P56, preferentially in cerebral cortex, and these young adult Olig2 KO mice showed anxiety-like behavior, motor skill learning deficit and cognitive deficit. Moreover, Olig2 CKO mice exhibited earlier social avoidance behavior than the WT littermates under prolonged social isolation, indicating that myelin deficit may enhance risk of schizophrenia upon environmental stress attacking. Interestingly, enhancing oligodendrocyte generation and myelin repair by quetiapine or clemastine successfully reversed the above phenotype.

Discussion: Taking together, promoting myelin repair may present a new therapeutic strategy against schizophrenia.

26. NOVEL APPROACHES TO PSYCHOSIS RISK: MOVEMENT, STRESS MODULATION, REWARD AND LANGUAGE

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Overall Abstract: Research on psychosis risk now encompasses novel and innovative approaches for understanding not only positive symptoms, but also impairment in sensorimotor function, stress regulation, reward learning, and language. These include the use of machine learning and cluster analysis with resting state functional connectivity analyses, in vivo measures of dopamine function in response to stress, computational modeling,

and automated natural language processing analyses in collaboration with IBM.

First, Vijay Mittal will describe subtypes of clinical risk, identifying a group with aggregated measures of sensorimotor dysfunction, developmental markers, negative symptoms and cognitive deficits, who have a discrete pattern of corticostriatal connectivity.

Second, Romina Mizrahi will present her results from a study of dopamine response to stress in prefrontal cortex, using positron emission tomography, and correlations with cortisol release, across stages of illness, including schizophrenia and clinical risk, with healthy volunteers for comparison.

Third, James Waltz will present data on the computational processes that may underlie both positive and negative symptoms, in respect to dopamine-based signals of salience. These include aberrant or erratic salience signaling, as well as a decreased ability to identify relevant salient stimuli, which could impair reward learning and motivation. His cohort includes individuals with psychosis, and those at clinical risk for it, as well as non-psychosis patient controls.

Fourth, Cheryl Corcoran will describe the use of automated natural language processing (NLP), with machine learning (ML) to identify semantic and syntactic features that predict psychosis onset. She will show data on cross-validation of the classifier in a second risk cohort, and its correlation with demographics and manual linguistic features. Overall, there is an apparent norm of semantic coherence and syntactic complexity from which individuals with psychosis deviate, even prior to its onset.

Finally, the discussant will review these data in the context of his experience and ongoing leadership in the field of psychosis risk research, leading audience discussion, and outlining a roadmap for future research in the field.

26.1 MOTOR SUBTYPES AND PREDICTION OF COURSE IN PSYCHOSIS RISK YOUTH

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Background: Prominent etiological conceptions of psychosis implicate abnormal cortico-striatal circuits. Dysfunction in these critical systems, responsible for filtering information and modulating higher-order function, may account for heterogeneous presentations of symptoms and characteristics of psychosis. Collectively, a body of work from our group and from other teams indicates that evaluating select motor behaviors and abnormalities, which directly reflect function of these circuits, may be a useful method for understanding and predicting the neural underpinnings of psychosis. In the context of the psychosis risk period, partitioning clinical high-risk (CHR) youth based on objective behavior may help guide early detection and intervention efforts, and provide a novel perspective on different etiological pathways or patient subtypes.

Methods: Using an unsupervised machine learning approach, 69 CHR young adults were included in a K-means cluster analysis based on their performance on instrumental measures of psychomotor slowing, dyskinesia, and neurological soft signs (NSS)—distinct motor domains affected across the psychosis spectrum. We also recruited a group of 70 matched healthy controls (HC) for comparison. All participants were also assessed with a resting-state functional connectivity analysis (rsfMRI). The resulting CHR group clusters and HCs were then compared on positive and negative symptoms, multiple cognitive domains, and cortical-striatal seed based resting state analysis.

Results: Results of a 3-cluster solution suggest that there are subtypes of CHR individuals who show psychomotor slowing, average motor performance, and impairment on measures of dyskinesia as well as NSS domains for motor coordination, sequencing and sensory integration. The cluster of individuals showing dyskinesia and abnormal NSS also have more severe negative symptoms and impairment on a number of cognitive domains. Furthermore, the clusters of CHR individuals who show psychomotor

slowing and the cluster showing dyskinesia and abnormal NSS have different cortical-striatal connectivity compared to UHR who show average motor behavior and healthy controls.

Discussion: These results provide evidence for etiological theories highlighting altered cortico-striatal networks and the importance of examining motor behavior prior to the onset of psychosis. Taken together, this approach may reflect a novel strategy for promoting tailored risk assessment as well as future research developing individualized medicine.

26.2 CORTICAL STRESS REGULATION IS DISRUPTED IN SCHIZOPHRENIA BUT NOT IN CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: While striatal dopamine in psychosis and stress has been well studied, the role of dopamine in the prefrontal cortex (PFC) is poorly understood. To date no study has investigated the PFC dopamine response to stress exclusively in schizophrenia or its putative prodrome, even though medial PFC is known as a key area in stress regulation. The present study uses the high-affinity dopamine D2/3 receptor radiotracer [¹¹C]FLB457 and positron emission tomography (PET) together with a validated psychosocial stress challenge to investigate if the PFC dopamine response to stress is dysregulated in schizophrenia and clinical high risk (CHR) for psychosis. **Methods:** Fourteen antipsychotic-free patients with schizophrenia, 14 CHR and 12 matched healthy volunteers underwent two [¹¹C]FLB457 PET scans, one while performing a Sensory Motor Control Task (control) and another while performing the Montreal Imaging Stress Task (stress). PET data were analyzed using the Simplified Reference Tissue Model with non-displaceable binding potential (BPND) as outcome measure. Dopamine release was defined as percent change in BPND between control and stress scan (Δ BPND).

Results: We observed an increased dopamine release, indexed by Δ BPND, in the medial PFC in schizophrenia patients but not CHR compared to healthy volunteers. Further, associations between stress-induced dopamine release and increase in cortisol levels observed in healthy volunteers and CHR, were absent in schizophrenia, similar to associations with symptoms, distress and anxiety.

Discussion: These findings provide first direct evidence of a disrupted cortical dopamine-stress regulation in schizophrenia.

26.3 SALIENCE SIGNALING AND THE EMERGENCE OF PSYCHOPATHOLOGY IN YOUTH AT CLINICAL HIGH RISK FOR PSYCHOTIC ILLNESS

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Background: The early identification of people who appear to be at high risk for conversion to psychosis has become a central thrust of mental health research, with the hope that early intervention may alter the course of psychotic illness. Importantly, both positive and negative symptom dimensions have been found relate to risk for conversion in clinical high risk (CHR) populations. Neuroimaging work points to a role for dopamine

pathway activity in both the positive and negative symptoms of psychotic illness. A role for dopamine pathways in signaling various kinds of salience is well-established, and several authors have proposed that excessive dopamine transmission in the striatum might contribute to psychotic symptoms by bringing about erratic, or “aberrant”, salience signaling. By contrast, a reduced ability to identify salient events as such, and signal salience “adaptively”, could result in impairments in learning and motivation. I will describe results from a study in which we examined the impact of salient events on learning and behavior in adolescents and young adults, a subset of whom were identified as being at CHR for developing psychotic illness.

Methods: Participants were 98 adolescents and young adults (mean age = 16.1 ± 3.3 years), assessed clinically using the Structured Interview for Psychosis-Risk Syndromes (SIPS). Eighty-nine participants were receiving mental health services, with 30 of the 89 identified as CHR and 8 identified as already having a psychotic illness. We used two experimental paradigms to investigate the impact of salient events on learning and behavior: the probabilistic stimulus selection task (PSST; Frank et al., 2004) and the Salience Attribution Task (SAT; Roiser et al., 2009). Both adaptive and aberrant salience signals were operationalized in the context of each task. Successful performance of the PSST depends on the adaptive signaling of mismatches between expected and obtained outcomes, called reward prediction errors, which are one form of salient event. The SAT requires participants to respond as quickly as possible to a response prompt, which is preceded by conditioned stimuli that potentially predict reward availability for a fast response. The comparison of reaction time (RT) between responses following the frequently vs. infrequently rewarded conditioned stimuli offers a measure of adaptive salience coding with the expectation of faster RT for reward predicting stimuli. The comparison of RT between responses to the two levels of the irrelevant dimension offers a measure of aberrant salience coding with the expectation of equal RT for stimuli equally-predictive of reward. We assessed whether experimental measures of both adaptive and aberrant salience showed correspondences with SIPS ratings for symptoms along both the positive and negative dimensions.

Results: We observed significant correlations between multiple performance measures from the PSST and measures of both positive and negative symptoms. We found that positive symptom severity, in help-seeking youth, correlated positively with an implicit measure of aberrant salience from the SAT, and negatively with an explicit measure of adaptive salience.

Discussion: These results, consistent with our previous findings in both first-episode psychosis patients and patients with chronic schizophrenia, suggest that experimental measures of salience signaling may provide a psychosis risk signal in treatment-seeking youth. Further research is necessary to understand the potential predictive role of these measures for conversion to psychosis.

26.4 LANGUAGE DISTURBANCE AS A PREDICTOR OF PSYCHOSIS ONSET IN YOUTH AT ENHANCED CLINICAL RISK

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Background: Language offers a privileged view into the mind; it is the basis by which we infer others' thoughts. Subtle language disturbance is evident in schizophrenia prior to psychosis onset, including decreases in coherence and complexity, as measured using clinical ratings in familial and clinical high-risk (CHR) cohorts. Bearden et al previously used manual linguistic analysis of baseline speech transcripts in CHR to show that illogical and referential thinking, and poverty of content, predict later psychosis onset.